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Synchronization of Coupled Nonidentical Genetic Oscillators*

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The study on the collective dynamics of synchronization among genetic oscillators is essential for the understanding of the rhythmic phenomena of living organisms at both molecular and cellular levels. Genetic oscillators are biochemical networks, which can generally be modelled as nonlinear dynamic systems. We show in this paper that many genetic oscillators can be transformed into Lur'e form by exploiting the special structure of biological systems. By using control theory approach, we provide a theoretical method for analyzing the synchronization of coupled nonidentical genetic oscillators. Sufficient conditions for the synchronization as well as the estimation of the bound of the synchronization error are also obtained. To demonstrate the effectiveness of our theoretical results, a population of genetic oscillators based on the Goodwin model are adopted as numerical examples.

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I. INTRODUCTION

Elucidating cooperative behavior of synchronization of coupled genetic oscillators has important biological implications and potential engineering applications from both theoretical and experimental viewpoints, and it is also essential for the understanding of the rhythmic phenomena of living organisms at both molecular and cellular levels. So far many researchers have studied the synchronization in genetic networks from the aspects of experiment, numerical

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simulation and theoretical analysis. For instance, in [1], the authors experimentally investigated the synchronization of cellular clock in the suprachiasmatic nucleus (SCN); in [2] and [3], the collective dynamics of synchronization are theoretically studied in synthetic biological networks of identical genetic oscillators; and in [4], the mechanism of synchronization in a population of identical hysteretic genetic oscillators is analyzed. Biologically, the genetic oscillators, even in the same species, are usually nonidentical possibly due to asymmetrical nutrition conditions and fluctuated environments, and the nonidentical property can be modelled as parametric mismatches among oscillators. For example, in the suprachiasmatic nucleus (SCN), the periods of the circadian oscillators are not exactly the same, and it has been observed that isolated individual neurons are able to produce circadian oscillations with period ranging from 20 to 28 hours [5, 6]. In [7, 8], the synchronization for nonidentical genetic oscillators is examined numerically. Although many mathematical models have been developed to study the cooperative behaviors of cellular oscillation, there is no general theoretical method in analyzing the dynamics of the coupled genetic oscillators due to their inherent nonlinearity.

Genetic networks are biochemically dynamical systems, in which the nodes indicate the biochemicals, and the couplings represent the biochemical interactions [9, 10]. Mathematically many genetic oscillators can be expressed in the form of multiple additive terms, each of which particularly is of linear, Michaelis-Menten or Hill forms, such as the well-known Goodwin model [11, 12], repressilator [13], toggle switch [14], and the circadian oscillators [15]. From the synthetic biology viewpoint, genetic oscillators with only linear, Michaelis-Menten and Hill form terms can also be implemented easily. In this paper we explore such special structure of gene networks to show that these genetic oscillators can be transformed into Lur'e form and can be further analyzed by using Lur'e system method in control theory [16].

The aim of this paper is to provide a general theoretical method for analyzing the synchronization of coupled nonidentical genetic oscillators with the above-mentioned structure. In studying the synchronization of genetic oscillators (and other nonlinear systems), a general idea is to study the stability of the error equations among oscillators. However, there are two main difficulties for such method: (1) the difference of the oscillator dynamics usually cannot be written into a function of the state error; (2) due to the nonlinearity, there is no general efficient analysis method for the stability of the error system. We show in this paper that for genetic oscillators with the above-mentioned structure, we can overcome both of the above difficulties. Since coupled nonidentical oscillators usually cannot achieve complete synchronization, a synchronous error is required to evaluate the quality of the synchronization. In this paper, we present a theoretical result, which can not only guarantee the synchronization, but also estimates the bound of

the synchronization error. Besides, the obtained conditions can be represented in terms of linear matrix inequalities (LMIs) [17], which are very easy to be verified. Recently, it was found that many biological networks are complex networks with small-world and scale-free properties [18, 19]. Our method is also applicable to genetic oscillator networks with complex topology, directed and weighted couplings. To demonstrate the effectiveness of the theoretical results, we present two simulation examples of coupled Goodwin oscillators with linear and Michaelis-Menten couplings, respectively. Finally, several remarks on the extensions of the proposed method are discussed. Notation used in this paper as well as the detailed theoretical analysis are given in the Appendix.

II. METHODS AND RESULTS

Mathematical modelling provides a powerful tool for studying gene regulation processes in living organisms. Basically, there are two types of genetic network models, i.e., the Boolean model (or discrete model) and the differential equation model (or continuous model) [20, 21, 22]. In Boolean models, the activity of each gene is expressed in one of two states, ON or OFF, and the state of a gene is determined by a Boolean function of the states of other related genes. In the differential equation models, the variables describe the concentrations of gene products, such as mRNAs and proteins, as continuous values, which are more accurate and can provide detailed understanding of the dynamical behaviors of the gene regulation systems. In this paper, by adopting the differential equation models, we consider the following form of a general genetic oscillator:

$$\dot{y}(t) = Ay(t) + \sum_{i=1}^{l} B_i f_i(y(t)), \tag{1}$$

where $y(t) \in R^n$ represents the concentrations of proteins, RNAs and chemical complexes, A and B_i are matrices in $R^{n\times n}$, $f_i(y) = [f_{i1}(y_1(t)), \cdots, f_{in}(y_n(t))]^T$ with $f_{ij}(y_j(t))$ as a monotonic increasing or decreasing regulatory function, which usually is of the Michaelis-Menten or Hill form. Undoubtedly, many well-known genetic system models can be represented in this form, such as the Goodwin model [11, 12], the repressilator [13], the toggle switch [14], and the circadian oscillators [15]. In synthetic biology, genetic oscillators of this form can be implemented experimentally [23]. To make our method more understandable and to avoid unnecessarily complicated notation, we consider the following simplified model, in which there are only one increasing and one decreasing nonlinear terms in each equation of the genetic oscillator.

$$\dot{y}(t) = Ay(t) + B_1 f_1(y(t)) + B_2 f_2(y(t)), \tag{2}$$

where $Ay(t)$ includes the degradation terms and all the other linear terms in the genetic oscillator, $f_1(y(t)) = [f_{11}(y_1(t)), \cdots, f_{1n}(y_n(t))]^T$ with $f_{1j}(y_j(t))$ as a monotonic increasing function of the Hill form

$$f_{1j}(y_j(t)) = \frac{(y_j(t)/\beta_{1j})^{H_{1j}}}{1 + (y_j(t)/\beta_{1j})^{H_{1j}}},$$

and $f_2(y(t)) = [f_{21}(y_1(t)), \cdots, f_{2n}(y_n(t))]^T$ with $f_{2j}(y_j(t))$ as a monotonic decreasing function of the following form

$$f_{2j}(y_j(t)) = \frac{1}{1 + (y_j(t)/\beta_{2j})^{H_{2j}}}.$$

In the above equations, both H_{1j} and H_{2j} are the Hill coefficients. To avoid confusion, we let the jth column of $B_{1,2}$ be zeros if $f_{1j,2j} \equiv 0$. Since

$$f_{2j}(y_j(t)) = \frac{1}{1 + (y_j(t)/\beta_{2j})^{H_{2j}}} = 1 - \frac{(y_j(t)/\beta_{2j})^{H_{2j}}}{1 + (y_j(t)/\beta_{2j})^{H_{2j}}} \equiv 1 - g_j(y_j(t)),$$

by letting $f(.) = f_1(.)$, we can rewrite (2) as follows:

$$\dot{y}(t) = Ay(t) + B_1 f(y(t)) - B_2 g(y(t)) + B_2. \tag{3}$$

Obviously, f_i and g_i satisfy the following sector conditions

$$\begin{gathered} 0 \leq \tfrac{f_i(a) - f_i(b)}{a - b} \leq k_{1i}, \\ 0 \leq \tfrac{g_i(a) - g_i(b)}{a - b} \leq k_{2i}, \\ \forall a, b \in R\,(a \neq b); i = 1, \cdots, n, \end{gathered}$$

or equivalently,

$$\begin{gathered} (f_i(a) - f_i(b))[(f_i(a) - f_i(b)) - k_{1i}(a - b)] \leq 0, \\ (g_i(a) - g_i(b))[(g_i(a) - g_i(b)) - k_{2i}(a - b)] \leq 0, \\ \forall a, b \in R\,(a \neq b); i = 1, \cdots, n, \end{gathered} \tag{4}$$

It follows from the mean value theorem that for differentiable f_i and g_i, the above sector conditions correspond to

$$\begin{gathered} 0 \leq \tfrac{df_i}{da}(a) \leq k_{1i}, \\ 0 \leq \tfrac{dg_i}{da}(a) \leq k_{2i}, \\ \forall a \in R; i = 1, \cdots, n. \end{gathered} \tag{5}$$

Recall that a Lur'e system is a linear dynamic system, feedback interconnected to a static nonlinearity $f(.)$ that satisfies a sector condition [16]. Hence, the genetic oscillator (3) can be seen as a Lur'e system, which can be investigated by using the fruitful Lur'e system method in control theory. In the following, we first consider coupled identical genetic oscillators, and then extend the result to the nonidentical case.

We first analyze the following N linearly coupled genetic oscillators, in which each genetic oscillator is identical.

$$\dot{x}_i(t) = Ax_i(t) + B_1 f(x_i(t)) - B_2 g(x_i(t)) + B_2 + \sum_{j=1}^{N} G_{ij} D x_j(t),\ i = 1, \cdots, N \tag{6}$$

where $x_i(t) \in R^n$ is the state vector of the ith genetic oscillator (corresponds to $y(t)$ in Eq. (3)), $D \in R^{n\times n}$ defines the coupling between two genetic oscillators. $G = (G_{ij})_{N\times N}$ is the coupling matrix of the network, in which G_{ij} is defined as follows: if there is a link from oscillator j to oscillator i ($j \neq i$), then G_{ij} equals to a positive constant denoting the coupling strength of this link; otherwise, $G_{ij} = 0$; $G_{ii} = -\sum_{j=1}^{n} G_{ij}$. Matrix G defines the coupling topology, direction, and the coupling strength of the network.

Since in biological networks, the genetic oscillators are usually nonidentical, there are parametric mismatches among oscillators. Next, we consider the following network of N coupled nonidentical genetic oscillators:

$$\begin{aligned}\dot{x}_i(t) = (A + \Delta A_i(t))x_i(t) + (B_1 + \Delta B_{1i}(t))f(x_i(t)) - (B_2 + \Delta B_{2i}(t))g(x_i(t)) + (B_2 + \Delta B_2(t)) \\ + \textstyle\sum_{j=1}^{N} G_{ij} D x_j(t),\ i = 1, \cdots, N\end{aligned} \tag{7}$$

where $\Delta A_i, \Delta B_{1i}, \Delta B_{2i}$ are the mismatch matrices, which can be time-varying. We assume that the mismatch matrices $\Delta A_i(t), \Delta B_{1i}(t), \Delta B_{2i}(t)$ can be estimated by the following bounds, which are also reasonable for general biological systems.

$$\|\Delta A_i(t)\| \leq \alpha_1, \|\Delta B_{1i}(t)\| \leq \alpha_2, \|\Delta B_{2i}(t)\| \leq \alpha_3, \forall i.$$

We also assume that

$$\|x_i(t)\| \leq \delta_1, \|f(x_i(t))\| \leq \delta_2, \|g(x_i(t))\| \leq \delta_3, \forall i.$$

Since in genetic oscillators, $x_i(t)$ usually denotes the concentrations of mRNA, protein, neurotransmitter, etc., which are of limited values, and $f(.)$ and $g(.)$ are usually monotonic functions with saturated values, the above assumptions are also reasonable. The other parameters are defined as the same as those in the identical case.

For the above two network, i.e. Eq. (6) and (7), we mainly use Wu's method to analyze the synchronization [24], which can separate the effects of the coupling and the individual genetic oscillator dynamics. Based on Lyapunov method, we can obtain the following sufficient conditions for the synchronization of coupled identical genetic oscillators (Eq. (6)) and coupled nonidentical genetic oscillators (Eq. (7)) in Theorems 1 and 2, respectively. In the following theorems and hereafter, $K_1 = \mathrm{diag}(k_{11}, \cdots, k_{1n})$, $K_2 = \mathrm{diag}(k_{21}, \cdots, k_{2n})$, and matrix $U \in R^{N\times N}$ is defined as an irreducible matrices with zero row sums, whose off-diagonal elements are all non-positive. $\lambda_{min}(P)$ and $\lambda_{max}(P)$ represent the minimal and maximal eigenvalues of the matrix P respectively, and $\otimes$ indicates the Kronecker product, which is defined in Appendix.

Theorem 1: If there are matrices $P > 0$, $\Lambda_1 = \mathrm{diag}(\lambda_{11}, \cdots, \lambda_{1n}) > 0$, $\Lambda_2 = \mathrm{diag}(\lambda_{21}, \cdots, \lambda_{2n}) > 0$, $Q \in R^{n\times n}$, and $U \in R^{N\times N}$, such that the following matrix inequalities hold

$$\begin{aligned} M_1 &= \begin{bmatrix} PA + A^T P - Q - Q^T & PB_1 + K_1\Lambda_1 & -PB_2 + K_2\Lambda_2 \\ B_1^T P + K_1\Lambda_1 & -2\Lambda_1 & 0 \\ -B_2^T P + K_2\Lambda_2 & 0 & -2\Lambda_2 \end{bmatrix} < 0, \\ &(UG \otimes PD + U \otimes Q)^T + (UG \otimes PD + U \otimes Q) \leq 0, \end{aligned} \tag{8}$$

then the network (6) is asymptotically synchronous.

Theorem 2: If there are matrices $P > 0$, $\Lambda_1 = \mathrm{diag}(\lambda_{11}, \cdots, \lambda_{1n}) > 0$, $\Lambda_2 = \mathrm{diag}(\lambda_{21}, \cdots, \lambda_{2n}) > 0$, $Q \in R^{n\times n}$, $U \in R^{N\times N}$, and a positive real constant γ such that the following matrix inequalities hold

$$\begin{aligned} M_2 &= \begin{bmatrix} PA + A^T P - Q - Q^T + \gamma I & PB_1 + K_1\Lambda_1 & -PB_2 + K_2\Lambda_2 \\ B_1^T P + K_1\Lambda_1 & -2\Lambda_1 & 0 \\ -B_2^T P + K_2\Lambda_2 & 0 & -2\Lambda_2 \end{bmatrix} < 0, \\ &(UG \otimes PD + U \otimes Q)^T + (UG \otimes PD + U \otimes Q) \leq 0, \end{aligned} \tag{9}$$

then the network (7) is asymptotically synchronous with error bound

$$\sum_{i<j}(-U_{ij})\|x_i(t) - x_j(t)\|^2 \leq \frac{\beta^2}{\gamma^2}\frac{\lambda_{max}(P)}{\lambda_{min}(P)}\sum_{i<j}(-U_{ij})$$

where

$$\beta = 4(\alpha_1\delta_1 + \alpha_2\delta_2 + \alpha_3\delta_3 + \alpha_3)\lambda_{max}(P)$$

The proof of the above theorems are somewhat technical, and we defer the details to the Appendix. In Theorem 2, we not only give a sufficient condition for the synchronization, but also provide an estimation of the synchronization error bound. In this error bound estimation, we can select the form of the matrix U beforehand to obtain different error combinations. Specifically, if we choose the following form of U

$$U = \begin{bmatrix} N-1 & -1 & \cdots & -1 \\ -1 & 1 & & \\ \vdots & & \ddots & \\ -1 & & & 1 \end{bmatrix}$$

we can obtain the following synchronous error estimation:

$$\sum_{j=2}^{N}\|x_j(t) - x_1(t)\|^2 \leq (N-1)\frac{\beta^2}{\gamma^2}\frac{\lambda_{max}(P)}{\lambda_{min}(P)}.$$

It should be note that, since in each step, we used conservative estimations of the bounds, the estimated error bound may be much larger than the actual error. In other words, if accurate information on the parametric mismatches is known, we can have a better error estimation.

The first matrix inequality in (8) (or (9)) is an LMI, which can be easily verified by using convex optimization techniques, e.g., the interior point method [17], and by software packages, e.g., the MATLAB LMI Toolbox. If we choose the matrix U beforehand, the second matrix inequality in (8) (or (9)) is also an LMI. Furthermore, for two special cases, we have the following results [25]:

(1) When G is symmetric: Letting $U = -G$, the second matrix inequality in (8) (or (9)) can be rewritten as

$$-G^2 \otimes (PD + D^T P) - G \otimes (Q + Q^T) \leq 0,$$

which is equivalent to

$$\sigma_i (PD + D^T P) + (Q + Q^T) \leq 0, \text{for all nonzero eigenvalues } \sigma_i \text{ of } G.$$

(2) When D is symmetric and commutable with G: Letting $U = -(G + G^T)/2$, the second matrix inequality in (8) (or (9)) can be rewritten as

$$-\frac{1}{2}(G + G^T)^2 \otimes PD - \frac{1}{2}(G + G^T) \otimes (Q + Q^T) \leq 0,$$

which is equivalent to

$$2\sigma_i PD + (Q + Q^T) \leq 0, \text{for all nonzero real part } \sigma_i \text{ of the eigenvalues of } G.$$

Thus the second matrix inequality in (8) (or (9)) is also a lower dimensional LMI, which together with the first LMI can be verified easily.

Next, we use numerical examples to show the effectiveness of the theoretical results.

III. NUMERICAL EXAMPLES

To demonstrate the effectiveness of our theoretical methods, we study a population of coupled SCN neuron model oscillators. The single cell or genetic oscillator is described by the classical Goodwin model [11]. In this model, a clock gene mRNA (X) produces a clock protein (Y), which activates a transcriptional inhibitor (Z). Z inhibits the transcription of the clock gene, thus forming a negative feedback loop. In this paper, we assume that the light $L = 0$.

The oscillators coupled through the release and receiving of neurotransmitter among neurons. Similar to [8], the evolution equations for a network of N coupled nonidentical oscillators are given below:

$$\begin{aligned}
\dot{X}_i &= v_{i1}\tfrac{1}{1+Z_i^m} - v_{i2}X_i + KF,\\
\dot{Y}_i &= v_{i3}X_i - v_{i4}Y_i,\\
\dot{Z}_i &= v_{i5}Y_i - v_{i6}Z_i,\\
\dot{V}_i &= v_{i7}X_i - v_{i8}V_i,
\end{aligned} \tag{10}$$

where $v_{i1}, v_{i2}, v_{i3}, v_{i4}, v_{i5}, v_{i6}, v_{i7}, v_{i8}$ are positive constants, and $K > 0$ is the coupling strength. The variables X_i, Y_i, Z_i describe the dynamics of the oscillator in the ith neuron, and V_i describes the evolution of the neurotransmitter in the ith neuron. The release of the neurotransmitter is supposed to be fast with respect to the 24-h timescale of the oscillators and becomes homogeneous to establish an average neurotransmitter level, or a mean field F [8]

$$F = \frac{1}{N}\sum_{j=1}^{N} V_j.$$

Clearly, the individual Goodwin model is of the form (3), in which $f \equiv 0$, $B_1 = 0$, $g = [0, 0, Z_i^m/(1+Z_i^m), 0]^T$, B_2 is a 4×4 matrix with all zero entries except for $B_2(1,3) = v_{i1}$, and all the other terms are in the linear form. By plus and minus KV_i in the first equation of (10), we can get the coupling term $\frac{K}{N}\sum_{j=1}^{N}(V_j - V_i)$.

The purpose of this section is to demonstrate the effectiveness of the theoretical method, instead of mimicking the real SCNs. We consider a small size of network with $N = 10$ coupled oscillators, although there are $\sim 10^4$ neurons in the SCNs. The concentrations are expressed in nM, and the standard parameters are set as $m = 12, v_{i1} = 1\,nM/h, v_{i3} = v_{i5} = 1/h, v_{i7} = 0.2/h, v_{i2} = 0.3/h, v_{i4} = 0.22/h, v_{i6} = 0.15/h, v_{i8} = 2/h$ for all i, so that the period of the oscillator is approximately 24h, and the coupling strength is $K = 1$. It is known that the period of the Goodwin model is sensitive to the parameters v_{i2}, v_{i4}, v_{i6} [12]. The mismatches of v_{i2}, v_{i4}, v_{i6} are randomly distributed in $\pm 10\%$ around the above values of v_{i2}, v_{i4}, v_{i6}. In Fig. 1, when starting from the same initial values, we show the oscillation dynamics of the mRNA concentrations of the 10 uncoupled oscillators, which indicate that the periods of the oscillators are quite different. Submitting the above parameters to the corresponding matrices in the matrix inequalities (9) of Theorem 2, letting $U = -G$ and using MATLAB LMI Toolbox, we can easily find feasible solutions for (9), which indicate that the above all-to-all coupled network can achieve synchronization although it is not a complete synchronous state. In Fig. 2 (a), when starting from different initial values, we plot the time evolution of the mRNA concentrations (X_i) of all the oscillators. Fig. 2 (b) shows the synchronization error

$$J = \sum_{i=2}^{N}[(X_i - X_1)^2 + (Y_i - Y_1)^2 + (Z_i - Z_1)^2 + (V_i - V_1)^2].$$

which is gradually reduced with time evolution.

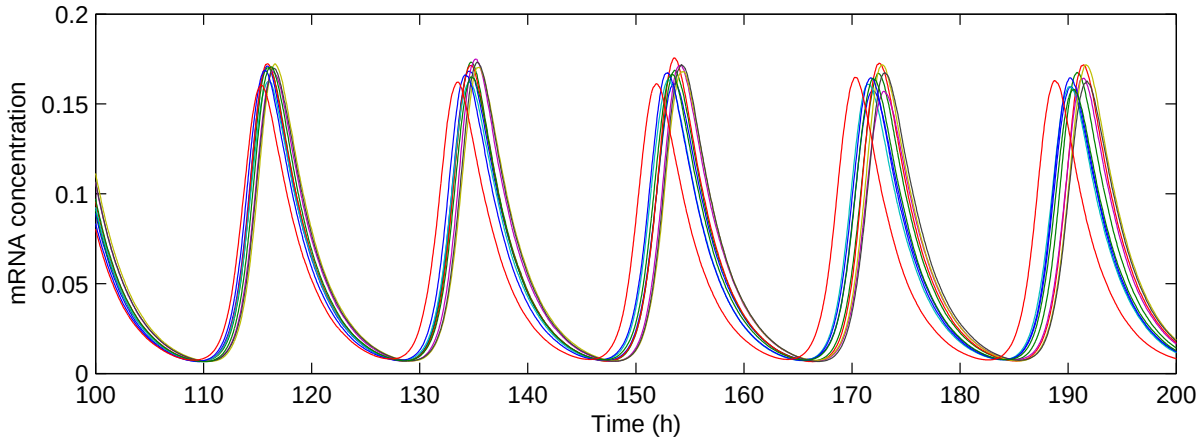

FIG. 1: Oscillation dynamics of the mRNA concentrations of the uncoupled oscillators with the same initial conditions.

Since there is a maximal activity of fully active promoters, in [8], the authors considered a Michaelis-Menten form of coupling term, that is, in (10) replacing KF by $K\frac{F}{1+F}$. Our theoretical results in Theorems 1 and 2 are also applicable for this case. Specifically, we may have different methods to treat the coupling term. One of the simplest ways is explained as follows: Since the coupling term $K\frac{F}{1+F}$ is the same for all oscillators and U is zero row sums, it is easy to show that the product of $U \otimes P$ and the vector of the coupling terms (containing the coupling terms of all the oscillators) is zero. By using the same analysis as that of Theorem 2, it is easy to show that the synchronization condition is only the first LMI in Theorem 2 with $Q = 0$. For the Michaelis-Menten coupling, Figs. 3 (a) and 3 (b) show the time evolution of the mRNA concentrations and the synchronization error, respectively. Figs. 2 and 3 indicate that the coupled oscillators are indeed synchronized with small error bounds, which confirms the theoretical results.

IV. CONCLUSION AND OUTLOOK

In this paper, we presented a theoretical method for analyzing the synchronization of coupled nonidentical genetic oscillators based on control theory approach. The purpose of this paper is not to provide a general theory for all genetic oscillator networks, but provide an efficient method for genetic oscillator networks that can be expressed in the form of (1). In addition, the sufficient conditions for the synchronization were also derived based on LMI formalism, which can be easily verified numerically. Although the method is proposed for genetic oscillator networks, it is also applicable to other biochemical and neuronal networks of the form. To make the theoretical method more

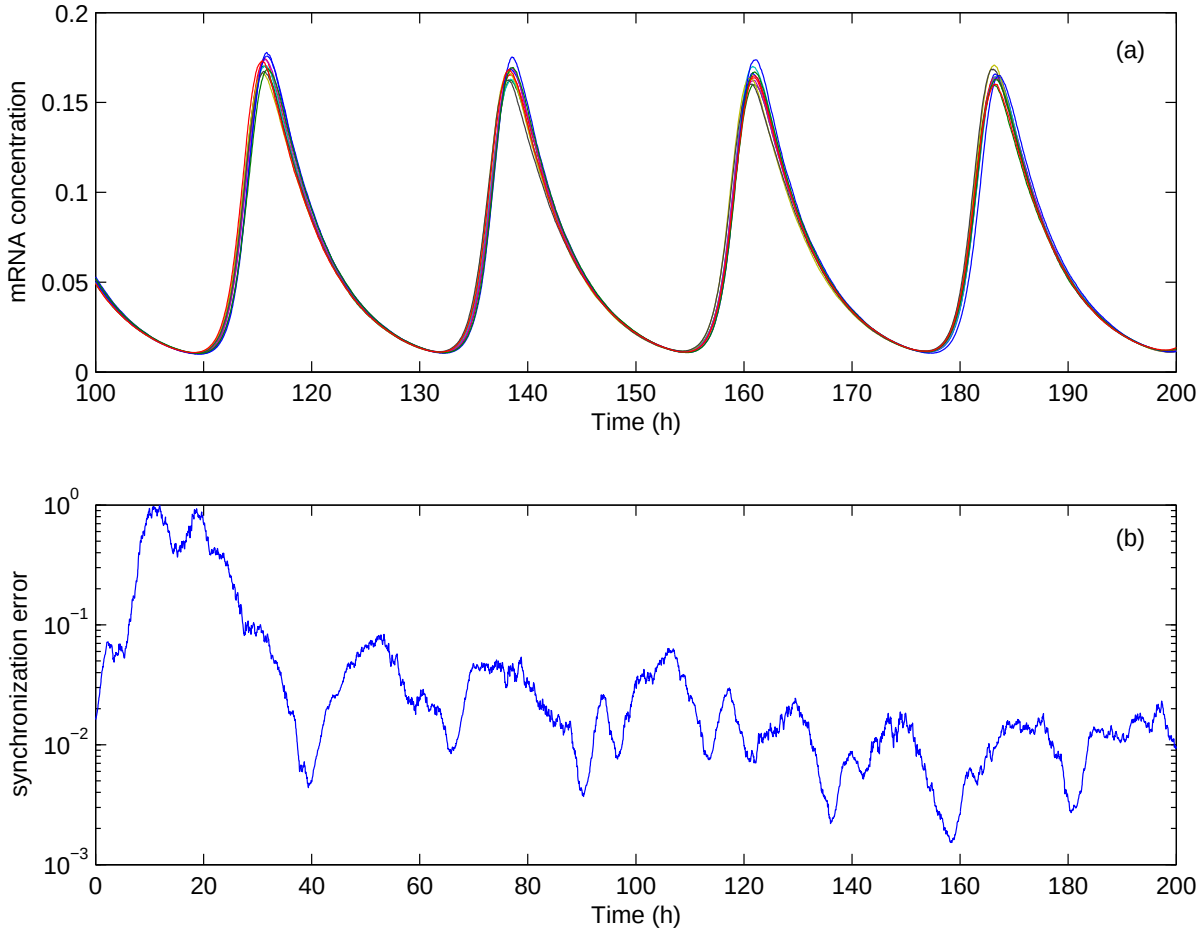

FIG. 2: Time evolution of Goodwin models with linear coupling. (a)The time evolution of the mRNA concentrations of the oscillators; (b) The time evolution of the synchronization error.

understandable and to avoid unnecessarily complicated notation, we discussed only on some simplified forms of the genetic oscillators, but more general cases and extensions regarding this topic can be studied in a similar way, for example:

1. The theoretical results can be easily extended to the general form of genetic oscillators with more than 2 nonlinear terms in each equation as shown in (1).

2. The genetic oscillator model (3) can be extended to a more general case such that f_i and g_i, the components of $f(y(t))$ and $g(y(t))$, are functions of $y(t)$, instead of $y_i(t)$. For this case, we only require that

$$0 \leq \frac{f_i(a)-f_i(b)}{c_{1i}^T(a-b)} \leq k_{1i}$$
$$0 \leq \frac{g_i(a)-g_i(b)}{c_{2i}^T(a-b)} \leq k_{2i}$$
$$\forall a, b \in R^n\,(a \neq b); i = 1, \cdots, n$$

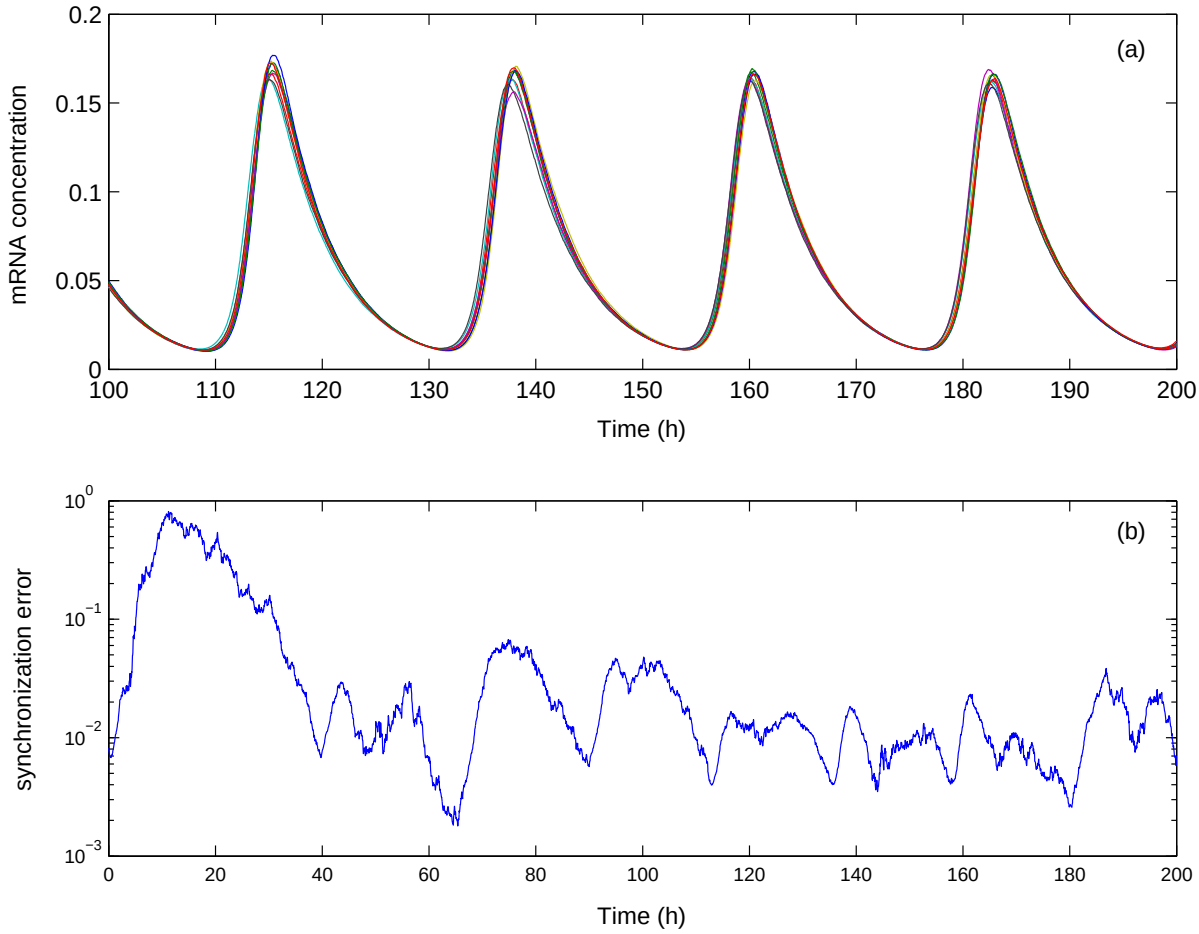

FIG. 3: Time evolution of Goodwin models with Michaelis-Menten coupling. (a)The time evolution of the mRNA concentrations of the oscillators; (b) The time evolution of the synchronization error.

where $c_{1i}, c_{2i} \in R^n$ are arbitrary nonzero real vectors. Moreover, f_i and g_i can be of more complex forms (non-Hill form) and non-differentiable provided that they satisfy sector conditions.

3. Genetic oscillators who have a few terms that are not in linear, Michaelis-Menten and Hill forms, can also be analyzed similarly by using our method. For example, in the mammalian circadian clock model [26], there are a few product terms (of the form xy) besides the three kinds of terms. We can treat these terms as follows: Since

$$x_1y_1 - x_2y_2 = x_1(y_1 - y_2) + y_2(x_1 - x_2), \text{ and } \frac{x_1(y_1 - y_2)}{y_1 - y_2} \leq max(x_1), \frac{y_2(x_1 - x_2)}{x_1 - x_2} \leq max(y_2),$$

then we can treat these terms similarly as those that satisfies the sector condition. Although such manipulation introduces additional conservation, the conservation is assumed to be limited since most terms in the model are of the three kind of terms.

In addition to the nonlinear and coupling properties, genetic networks are intrinsically noisy [27, 28, 29, 30, 31], and with significant time delays [32, 33]. Future works regarding this topic also include the extension of our method to the case with noise perturbations and time delays.

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GLOSSARY

Gene regulatory network or genetic network: A gene regulatory network is a collection of DNA segments in a cell which interact with each other and with other substances in the cell, thereby governing the rates at which genes in the network are transcribed into mRNA.

Circadian rhythm: Circadian rhythm is the name given to the roughly 24 hour cycles shown by physiological processes in plants, animals, fungi and cyanobacteria.

Synchronization: synchronization of dynamical systems refers to a process wherein two (or many) systems (either identical or nonidentical) adjust a given property of their motion to a common behavior due to a coupling or to a forcing (periodical or noisy).

Lur'e system: a Lur'e system is a linear dynamic system, feedback interconnected to a static nonlinearity that satisfies a sector condition.

APPENDIX

A. Notations:

Throughout this paper, A^T denotes the transpose of a square matrix A. The notation $M > (<) 0$ is used to define a real symmetric positive definite (negative definite) matrix. R^m denotes the m-dimensional Euclidean space; and $R^{n\times m}$ denotes the set of all $n \times m$ real matrices. In this paper, if not explicitly stated, matrices are assumed to have compatible dimensions. $\|\cdot\|$ stands for the usual L_2 norm of a vector, or the usual spectral norm of a square

matrix. Matrix $U \in R^{N\times N}$ is defined as an irreducible matrices with zeros row sum, whose off-diagonal elements are all non-positive. The Kronecker product $A \otimes B$ of an $n \times m$ matrix A and a $p \times q$ matrix B is the $np \times mq$ matrix defined as

$$A \otimes B = \begin{bmatrix} A_{11}B & \cdots & A_{1m}B \\ \vdots & \ddots & \vdots \\ A_{n1}B & \cdots & A_{nm}B \end{bmatrix}$$

B. Theoretical Analysis of the Synchronization

Proof of Theorem 1: We let $x(t) = [x_1^T(t), \cdots, x_N^T(t)]^T \in R^{Nn\times 1}$, and define a Lyapunov function of the following form:

$$V(x(t)) = x^T(t)(U \otimes P)x(t) \tag{11}$$

According to [24] (pp.136-137), $V(x(t))$ is equivalent to the following form

$$V(x(t)) = \sum_{i<j}(-U_{ij})(x_i(t) - x_j(t))^T P(x_i(t) - x_j(t)).$$

Hence, if the time derivative of $V(x(t))$ along the trajectories of (6) is negative, then according to Lyapunov's direct method, the genetic oscillators will achieve synchronization.

Calculating the time derivative of $V(x(t))$, we have

$$\begin{aligned} \dot{V}(x(t)) = \; & 2\textstyle\sum_{i<j}(-U_{ij})(x_i(t) - x_j(t))^T P[(A-T)(x_i(t) - x_j(t)) + B_1(f(x_i) - f(x_j)) - B_2(g(x_i) - g(x_j))] \\ & +2x^T(t)(U \otimes P)(G \otimes D + I \otimes T)x(t) \end{aligned} \tag{12}$$

where $T \in R^{n\times n}$ is an arbitrary real matrix. For all $i, j\,(i \neq j)$, we have

$$\begin{aligned} & L_{ij} = 2(x_i(t) - x_j(t))^T P[(A-T)(x_i(t) - x_j(t)) + B_1(f(x_i(t)) - f(x_j(t))) - B_2(g(x_i(t)) - g(x_j(t)))] \\ & \leq 2(x_i(t) - x_j(t))^T P(A-T)(x_i(t) - x_j(t)) + 2(x_i(t) - x_j(t))^T P B_1(f(x_i(t)) - f(x_j(t))) \\ & \quad -2(x_i(t) - x_j(t))^T P B_2(g(x_i(t)) - g(x_j(t))) \\ & \quad -2\textstyle\sum_{l=1}^{n}\lambda_{1l}(f_l(x_{il}(t)) - f_l(x_{jl}(t)))[(f_l(x_{il}(t)) - f_l(x_{jl}(t))) - k_{1l}(x_{il}(t) - x_{jl}(t))] \\ & \quad -2\textstyle\sum_{l=1}^{n}\lambda_{2l}(g_l(x_{il}(t)) - g_l(x_{jl}(t)))[(g_l(x_{il}(t)) - g_l(x_{jl}(t))) - k_{2l}(x_{il}(t) - x_{jl}(t))] \end{aligned}$$

By letting $Q = PT$, we have

$$L_{ij} = \xi_{ij}(t)M_1\xi_{ij}(t) < 0$$

for all i, j. $\xi_{ij} = [(x_i(t) - x_j(t))^T, (f(x_i(t)) - f(x_j(t)))^T, (g(x_i(t)) - g(x_j(t)))^T]^T \in R^{3n\times 1}$. Therefore, the first term of (12) is negative except for $x_i(t) = x_j(t)$, $\forall i, j$. By letting $Q = PT$, $(U \otimes P)(G \otimes D + I \otimes T)^T + (U \otimes P)(G \otimes D + I \otimes T)$ is equivalent to the second matrix inequality in (8), which means that the second term of (12) is non-positive. We have $\dot{V}(x(t)) < 0$ in (12). Thus the Theorem 1 is proved. □

Next, we consider the case of coupled nonidentical genetic oscillators (7). In [34], the authors studied the robust synchronization of master-slave coupled two nonidentical chaotic systems of the Lur'e form. Here we extend the result to the case of complex networks, and apply it to the coupled nonidentical genetic oscillators.

Proof of Theorem 2: We also use the Lyapunov function (11). By calculating the time derivative of $V(x(t))$, we have

$$\begin{aligned}\dot{V}(x(t)) = \; & 2\textstyle\sum_{i<j}(-U_{ij})(x_i(t) - x_j(t))^T P[((A + \Delta A_i(t)) - T)(x_i(t) - x_j(t)) \\ & +(B_1 + \Delta B_{1i}(t))(f(x_i) - f(x_j)) - (B_2 + \Delta B_{2i}(t))(g(x_i) - g(x_j)) + (\Delta B_{2i} - \Delta B_{2j})] \\ & +2x^T(t)(U \otimes P)(G \otimes D + I \otimes T)x(t)\end{aligned} \tag{13}$$

By letting $Q = PT$, it is easy to know the second term is nonpositive, and for all i, j $(i \neq j)$, we have

$$\begin{aligned}& 2(x_i(t) - x_j(t))^T P[((A + \Delta A_i(t)) - T)(x_i(t) - x_j(t)) + (B_1 + \Delta B_{1i}(t))(f(x_i) - f(x_j)) \\ & \qquad -(B_2 + \Delta B_{2i}(t))(g(x_i) - g(x_j)) + (\Delta B_{2i} - \Delta B_{2j})] \\ & = 2(x_i(t) - x_j(t))^T P[(A - T)(x_i(t) - x_j(t)) + B_1(f(x_i(t)) - f(x_j(t))) - B_2(g(x_i(t)) - g(x_j(t)))] \\ & \quad +2(x_i(t) - x_j(t))^T P[\Delta A_i(t)x_i(t) - \Delta A_j(t)x_j(t) + \Delta B_{1i}(t)f(x_i(t)) - \Delta B_{1j}(t)f(x_j(t)) \\ & \quad -\Delta B_{2i}(t)g(x_i(t)) + \Delta B_{2j}(t)g(x_j(t)) + \Delta B_{2i}(t) - \Delta B_{2j}(t)] \\ & \leq \xi_{ij}(t)M_1\xi_{ij}(t) + 2\|x_i(t) - x_j(t)\|\lambda_{max}(P)(2\alpha_1\delta_1 + 2\alpha_2\delta_2 + 2\alpha_3\delta_3 + 2\alpha_3) \\ & = \xi_{ij}(t)M_2\xi_{ij}(t) - \gamma\|x_i(t) - x_j(t)\|^2 + \beta\|x_i(t) - x_j(t)\| \\ & < -\gamma\|x_i(t) - x_j(t)\|^2 + \beta\|x_i(t) - x_j(t)\|\end{aligned}$$

where $\xi_{ij}(t)$ and M_1 are the same as those defined in the Proof of Theorem 1. We have $\dot{V}(x(t)) < 0$ if $\|x_i(t) - x_j(t)\| \geq \beta/\gamma$. Since

$$\lambda_{min}(P)\sum_{i<j}(-U_{ij})\|(x_i(t) - x_j(t))\|^2 \leq V(x(t)) \leq \lambda_{max}(P)\sum_{i<j}(-U_{ij})\|(x_i(t) - x_j(t))\|^2,$$

we have

$$\lambda_{min}(P)\sum_{i<j}(-U_{ij})\|(x_i(t) - x_j(t))\|^2 \leq \lambda_{max}(P)\frac{\beta^2}{\gamma^2}\sum_{i<j}(-U_{ij}).$$

Thus we obtain the error bound in Theorem 2. Note that $\frac{\lambda_{max}(P)}{\lambda_{min}(P)}$ is the conditional number of matrix P. □

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